Metal Free Regioselective Chloroazidation of Internal Alkynes

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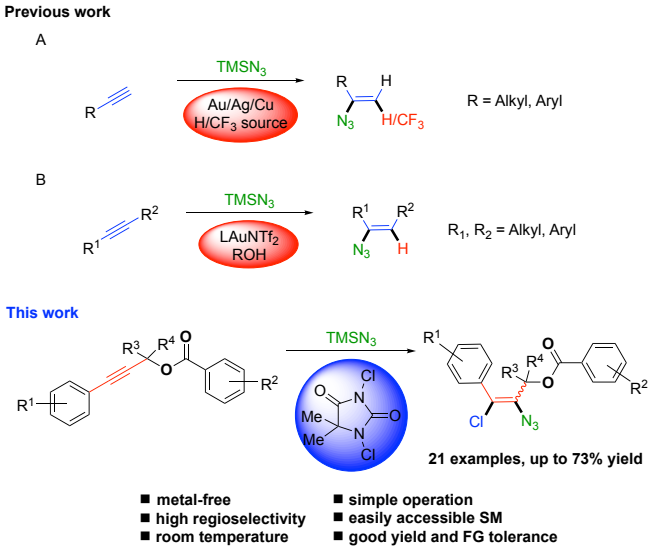
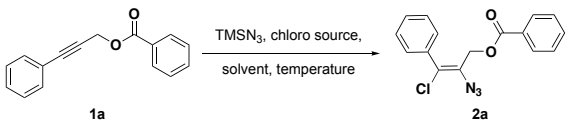
Abstract: A metal-free, room temperature protocol for the regioselective chloroazidation of internal alkynes is disclosed. The reactions of internal alkynes with trimethylsilyl azide (TMS-N_3) in the presence of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) afforded the corresponding chloroazidoalkenes in good yields. This reaction has good functional group tolerance and is operationally simple.

Vinyl azides are energetic intermediates towards bioactive nitrogen-containing molecules, such as synthetically and biologically valuable 2*H*-azirines, formed *via* a reactive vinyl nitrene species.[1,2] Therefore, procedures for the simple preparation of vinyl azides are highly desirable. Easily available alkynes have been shown to serve as an ideal starting point and elegant metal catalytic methods of hydroazidation and trifluoromethylazidation of unhindered terminal alkynes have been developed during the past decade (Scheme **1A**).[3,4] Very recently, Zhang and co-workers pioneered the hydroazidation of more challenging internal alkynes using a ligand-accelerated gold-catalyzed protocol (Scheme **1B**).[5] Extending this concept to the haloazidation of alkynes would give access to highly valuable bifunctional haloazidoalkenes. To date, this transformation has been relatively underexplored, presumably due to the high intrinsic reactivity of the compounds involved: haloazidoalkenes, halogen azide species or reagents that serve as a halogen source, all of which tend to form various other products such as nitriles,[6] α,α-diazidoketones,[7] α,α-dihaloketones[8] and diketones.[9] Transition-metal free reactions of unreactive substrates have attracted considerable attention from the synthetic community, as they are often less costly, more environmentally friendly and, most importantly, avoid possible transition metal impurities in pharmaceutical products.[10,11] Therefore, in order to enlarge the library of functionalized vinyl azides, we have developed a metal-free protocol for the convenient preparation of chloroazidoalkenes from internal alkynes at room temperature. The formed chloroazidoalkenes can easily be converted into the corresponding triazoles *via* click chemistry or into a new type of chloro-2*H*-azirines under thermal conditions. Chloro-2*H*-azirines provide new possibilities for biological studies of 2*H*-azirines and their transformation into more complex skeletons. It was envisaged that treatment of an internal alkyne with an appropriate combination of an azide donor and a chloro source would lead to the desired chloroazidoalkene. Initially, this reaction was studied using the simple alkyne 3-phenylprop-2-yn-1-yl benzoate **1a** as a substrate, $TMSN_3$ (1.2 eq) as the azide source and 1,2-dichloroethane as the solvent. After screening of various chloro sources (Table 1, entries 1-4), we found the most promising results with 2,4-*N*-chlorosaccharin or 1,3-dichloro-5,5-dimethylhydantoin (DCDMH),[12] which afforded the desired product **2a** as a single (*Z*)-isomer in 26% and 35% yield, respectively. Encouraged by this result, we tested different solvents (Table 1, entries 4-7) and identified CH_2Cl_2 as the best choice. Attempts to improve the yield of **2a** by increasing the amount of chloro source were unsuccessful (entry 8), but increasing the number of equivalents of $TMSN_3$ gave a slight improvement (entry 9). Finally, by increasing the amount of DCDMH (2.2 eq) and $TMSN_3$ (4.4 eq), full conversion of the starting material was observed and the yield increased to 57% (entry 10). Further optimization by varying the concentration (entries 11-12) or temperature (entries 13-14) did not lead to any improvement in the yield.



Scheme 1. Functionalized Vinyl Azides Synthesis via Alkynes

Table 1. Optimization of the Reaction Conditions



entry	chloro source (equiv)	$TMSN_3$ (equiv)	solvent	Yield[e] (%)
1	NCS (1.2)	(1.2)	DCE	0
2	TCICA (1.2)	(1.2)	DCE	0
3	2,4 *N*-chlorosaccharin (1.2)	(1.2)	DCE	26
4	DCDMH (1.2)	(1.2)	DCE	35
5	DCDMH (1.2)	(1.2)	CH_3CN	29
6	DCDMH (1.2)	(1.2)	pentane	0
7	DCDMH (1.2)	(1.2)	CH_2Cl_2	41
8	DCDMH (2.2)	(1.2)	CH_2Cl_2	38

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9	DCDMH (1.2)	(2.2)	CH_2Cl_2	45
10	**DCDMH (2.2)**	**(4.4)**	**CH_2Cl_2**	**57**
11[a]	DCDMH (2.2)	(4.4)	CH_2Cl_2	54
12[b]	DCDMH (2.2)	(4.4)	CH_2Cl_2	45
13[c]	DCDMH (2.2)	(4.4)	CH_2Cl_2	29
14[d]	DCDMH (2.2)	(4.4)	CH_2Cl_2	trace

General reaction conditions: **1a** (0.1 mmol, 1.0 equiv) in CH_2Cl_2 (0.6 ml) at 25 °C. Solvent volume used for *a*: 0.3 ml; for *b*: 1.2 ml. Reaction temperature for *c*: 0 °C; for *d*: 50 °C. *e*: isolated yield. NCS: *N*-chlorosuccinimide, TCICA: trichloroisocyanuric acid.

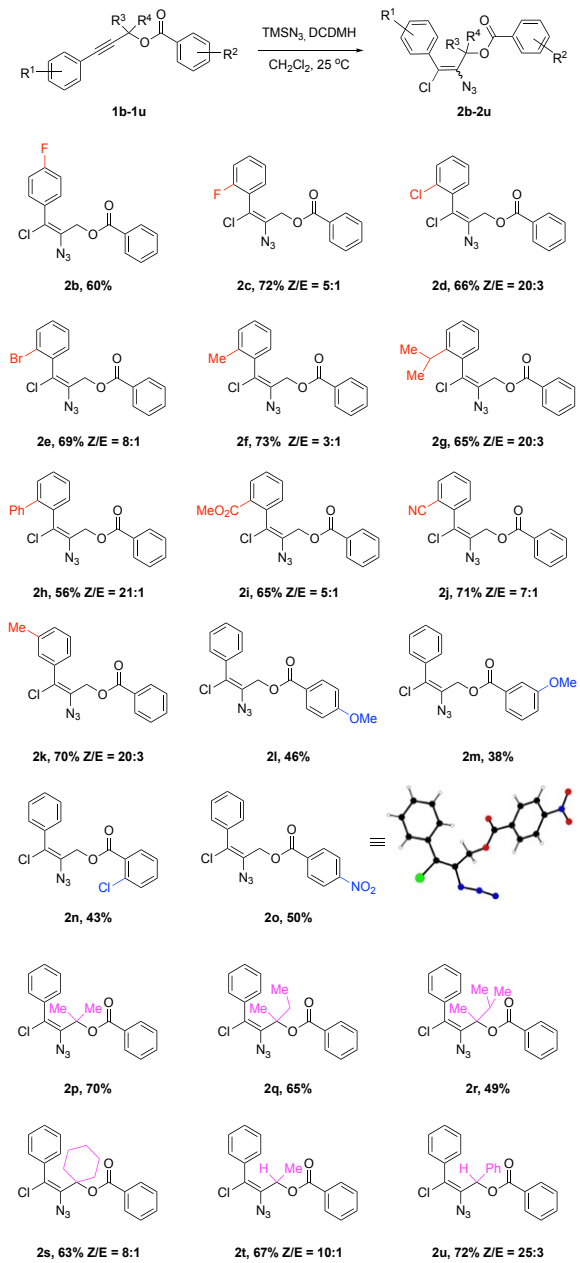
With the optimized conditions in hand (Table 1, entry 10), the substrate scope involving various alkynes was investigated. As shown in Scheme **2**, a range of R^1 substituents such as halides (**1b-1e**), alkyl (**1f-1g**, **1k**) and aryl (**1h**) groups, as well as an ester (**1i**) and a nitrile (**1j**), were tolerated at various positions on the phenyl ring and furnished **2b-2k** in 56-73% yield. It was noted that the (*E*)-isomer was observed in small amounts for ortho (**1c-1j**) or meta (**1k**) substituents. The structure of (*E*)-**2c** was confirmed by conversion to the corresponding triazole (*E*)-**3a** using click chemistry and single-crystal X-ray analysis of the formed product.[13,14,15]

Subsequently, the effect of the R^2 group was studied, as summarized in Scheme **2**. The electron-donating group OMe (**1l**, **1m**), a chloride substituent (**1n**) and the electron-withdrawing group NO_2 (**1o**) at different positions on the phenyl ring were tolerated and afforded the corresponding chloroazidoalkenes as single isomers in 38-50% yield. The structure of compound **2o** was unambiguously confirmed by single-crystal X-ray analysis. [15] Next, the effect of the R^3 and R^4 group was examined, as summarized in Scheme **2**. Both dialkyl (**1p-1s**), monoalkyl (**1t**) and monophenyl were tolerated and delivered the corresponding chloroazidoalkenes in 49-72% yield. The (*E*)-isomer was also observed in small amounts for **1s-1u**. Interestingly, internal alkynes are required for reactivity, which is in line with the iodoazidation reaction reported earlier. [8a]

To demonstrate the synthetic utility of the chloroazidoalkene products, **2o** was reacted with 1-ethynyl-4-methylbenzene in the presence of CuI and *N,N*-diisopropylethylamine (DIPEA) in CH_2Cl_2 at room temperature for 24 h to deliver the triazole **3b** in 63% yield (scheme 3); the structure of **3b** was confirmed by single-crystal X-ray analysis.[15] Furthermore, heating **2o** in toluene at 90 °C for 12 h afforded the chloro-2*H*-azirine **4a** in 79% yield as a single isomer. However, the structure obtained by single-crystal X-ray analysis revealed migration of the chloride away from the benzylic position.[15] Interestingly, the same phenomenon was observed for chloroazidoalkenes (*Z*)-**2a**, (*Z/E*)-**2c** and (*Z/E*)-**2f**, which, upon heating, afforded the corresponding chloro-2*H*-azirines **4b** (76%), **4c** (88%) and **4d** (73%), respectively. For this migration process we propose the intermediate of a two π-electron azacyclopropenyl (azirinium) ion, as illustrated in Scheme **3**.[16] Neighboring group participation by the benzoate might facilitate the reaction and the observed regioselectivity.

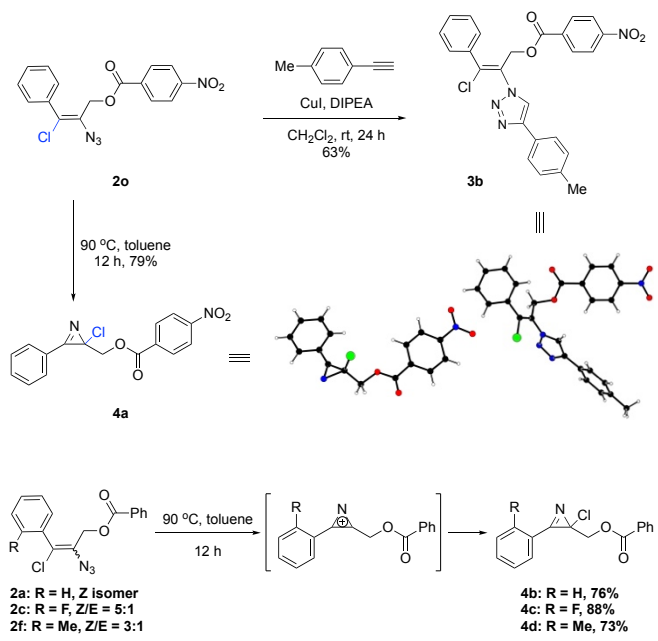
There are hardly any literature reports for the preparation of chloro-2*H*-azirines.[16,17] and our method is an easy two-step procedure starting from readily available alkynes. To the best of our knowledge, this is the first example of a chloro-2*H*-azirine bearing a neighbouring CH_2OR group. As 2*H*-azirines are prevalent in medicines and crop protection agents,[18] this new type of chloro-2*H*-azirine may provide a new scaffold for biologically active compounds. Meanwhile, these azirines, which process a good leaving group at the C2 position, are of special interest as precursors for a variety of reactions involving either retention of the azirine system (Cl displacement by various nucleophiles such as MeOH, CH_3S^-, N_3^- and AcO^-) or ring expansion to more complex skeletons (formation of diazepines, oxazines, quinoxalines, triazines, *etc*).[19]

Scheme 2. Substrate Scope of Alkynes.

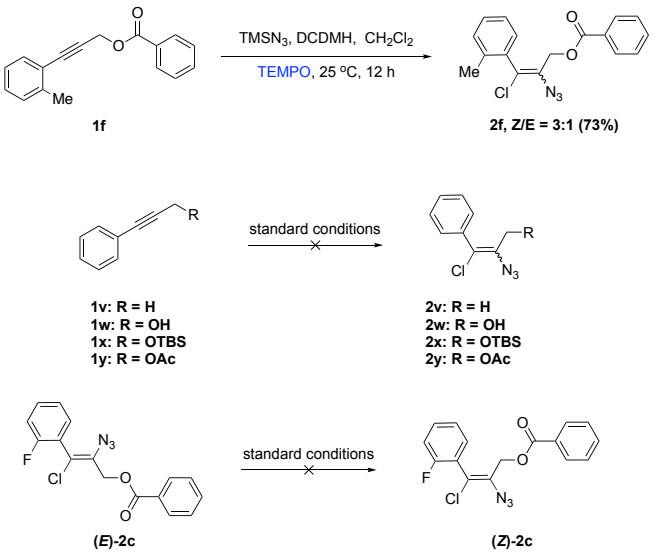


General reaction conditions: **1b-1u** (0.1 mmol, 1.0 equiv), DCDMH (0.22 mmol, 2.2 equiv), $TMSN_3$ (0.44 mmol, 4.4 equiv), CH_2Cl_2 (0.6 mL), 25 °C, 12-16 h under nitrogen, isolated yield.

Scheme 3. Synthetic Transformation of Chloroazidoalkenes



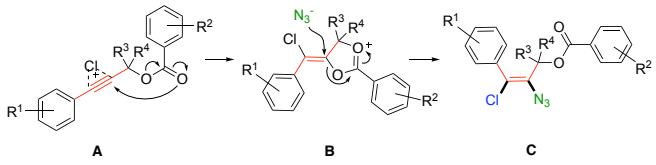
Scheme 4. Mechanistic Studies.



To gain insight into the mechanism of the chloroazidation of internal alkynes, several control experiments were carried out, as shown in Scheme **4**. According to previous reports, the reaction of the ClN_3 species with styrene could proceed *via* a radical pathway under certain conditions.[20] However, this reaction was not inhibited by the presence of the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), thus suggesting the absence of radical species in the reaction pathway. No formation of the corresponding chloroazidoalkenes was observed when replacing the benzoate group with H (**1v**), OH (**1w**), OTBS (**1x**) or OAc (**1y**) substituents, and this, along with the unique regioselectivity of the final product, implied neighboring group participation of the benzoate group in the reaction pathway. Yanada and co-workers demonstrated isomerization of the C=C double bond during the iodoazidation process of alkynes, after the isolated mixture of *E* and *Z* isomers was exposed to the same reaction conditions.[8a] However, using our standard reaction conditions, no isomerization of the double bond of isolated (*E*)-**2c** took place after stirring for 12 h. The formation of the corresponding chloroazidoalkenes of dialkyl (**1p**-**1s**) substrates excludes the existence of allene intermediates.

On the basis of the results obtained, the possible reaction pathway is outlined in Scheme **5**. Firstly, DCDMH reacts with the alkyne to form a chlorirenium ion **A**, followed by intramolecular attack of the benzoate group to give the oxocarbenium ion **B**. Such an intermediate would explain the participation of the benzoate in the reaction. Finally, the azide liberated from $TMSN_3$ attacks the oxocarbenium ion **B** to deliver the chloroazidoalkene product. The *Z*/*E* selectivity may be due to the instability of the *E* isomer under the reaction conditions and is still under investigation.

Scheme 5. A Possible Reaction Pathway.



In conclusion, we have developed a novel metal-free chloroazidation of internal alkynes promoted by TMS-N_3 and DCDMH. The presented reaction proceeds under mild reaction conditions, with good functional group tolerance and in good yield. In addition, we successfully showed that the synthesized chloroazidoalkenes can easily be converted into a new type of chloro-2H-azirines, which might find application in medicinal and synthetic chemistry. Investigation of their biological activities and transformations into more complex skeletons is ongoing in our laboratory.

Keywords: metal-free • chloroazidation • regioselective • internal alkynes •

[1] For selected reviews and books, see: a) G. L'Abbe, Reactions of vinyl azides. *Angew. Chem. Int. Ed.* **1975**, *14*, 775. b) B. Hu, S. G. DiMagno, *Org. Biomol.Chem.* **2015**, *13*, 3844. c) H. Hayashi, A. Kaga, Chiba, S. *J. Org. Chem.* **2017**, *82*, 11981. d) K. Banert, in Organic Azides: Syntheses and Applications; S. Bräse, K. Banert, Eds., John Wiley & Sons Ltd.: Chichester, 2010.

[2] For selected examples, see: a) Y. Wang, K. K. Toh, J. Lee, S. Chiba, *Angew. Chem. Int. Ed.* **2011**, *50*, 5927. b) Z. Zhu, X. Tang, X. Li, W. Wu, G. Deng, H. Jiang, *J. Org.Chem.* **2016**, *81*, 1401. c) J. E. Curiel Tejeda, L. C. Irwin, M. A. Kerr, *Org. Lett.* **2016**, *18*, 4738. d) Z. Zhu, X. Tang, J. Li, X. Li, W. Wu, G. Deng, H. Jiang, *Org. Lett.* **2017**, *19*, 1370.

[3] a) T. Shen, T. Wang, C. Qin, N. Jiao, *Angew. Chem., Int. Ed.* **2013**, *52*, 6677. b) Z. Liu, J. Liu, L. Zhang, P. Liao, J. Song, X. Bi, *Angew. Chem., Int. Ed.* **2014**, *53*, 5305. c) Z. Liu, P. Liao, X. Bi, *Org. Lett.* **2014**, *16*, 3668.

[4] a) F. Wang, N. Zhu, P. Chen, J. Ye, G. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 9356.

[5] X. Li, S. Liao, Z. Wang, L. Zhang, *Org. Lett.* **2017**, *19*, 3687.

[6] N. Okamoto, M. Ishikura, R. Yanada, *Org. Lett.* **2013**, *15*, 2571.

[7] a) R. F. Merritt, J. K. Ruff, *J. Org. Chem.* **1965**, 30, 328. b) J. M. D'Oyley, A. E. Aliev, T. D. Sheppard, *Angew. Chem., Int. Ed.* **2014**, 53, 10747. c) J. Liu, W. Li, C. Wang, W. Li, Z. Li, *Tetrahedron Lett.* **2011**, *52*, 4320.

[8] a) N. Okamoto, T. Sueda, H. Minami, Y. Miwa, R. Yanada, *Org. Lett.* **2015**, *17*, 1336. b) C. Gao, J. Li, J. Yu, H. Yang, H. Fu, *Chem. Commun.* **2016**, *52*, 7292.

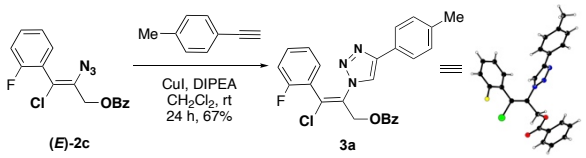
[9] a) M. Niu, H. Fu, Y. Jiang, Y. Zhao, *Synthesis* **2008**, *18*, 2879.

[10] For selected reviews, see: a) A. Ibrar, I. Khan, N. Abbas, U. Farooq, A. Khan, *RSC Adv.,* **2016**, *6,* 93016. b) G. A Ramann, B. J. Cowen, *Molecules* **2016**, *21*, 986.

[11] For selected examples, see: a) B. Huang, F. Zhang, G. Yu, Y. Song, X. Wang, M. Wang, Z. Gong, R. Su, Jia, Y. *J. Med. Chem.* **2016**, *59*, 3953. b) F. Zhang, Y. Jia, *Tetrahedron* **2009**, *65*, 6840. c) M. Li, S. Berritt, L. Matuszewski, G. Deng, A. Pascual-Escudero, G. B. Panetti, M. Poznik, X. Yang, J. J. Chruma, P. J. Walsh, *J. Am. Chem. Soc.* **2017**, *139*, 16327. d) J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005. e) M. Nogami, K. Hirano, M. Kanai, C. Wang, T. Saito, K. Miyamoto, A. Muranaka, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 12358. f) K. Kikushima, M. Grellier, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2017**, *56*, 16191. g) Y. Tu, X. Zeng, H. Wang, J. Zhao, *Org. Lett.* **2018**, *20*, 280.

[12] D. C. Whitehead, R. J. Staples, B. Borhan, *Tetrahedron Lett.* **2009**, *50*, 656.

[13]



(*E*)-2c 3a

[14] a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302. b) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952. c) R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613. d) R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.* **1967**, *100*, 2494.

[15] CCDC 1824871 (**2o**), CCDC 1824872 (**3a**), CCDC 1824873 (**3b**), CCDC 1824874 (**4a**), contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/structures.

[16] J. Ciabattoni, M. Cabell. Jr, *J. Am. Chem. Soc.* **1971**, *93*, 1482.

[17] a) T. M. V. D. Pinho e Melo, C. S. J. Lopes, A. L. Cardoso, A. M. d'A Rocha Gonsalves, *Tetrahedron* **2001**, *57*, 6203. b) G. A. Shavaleeva, N. A. Ivanova, F. G. Usmanova, R. R. Akhmetvaleev, M. S. Miftakhov, *Russ. J. Org. Chem.* **2004**, *40*, 1521. c) J. R. Fotsing, K. Banert, *Synthesis* **2006**, **2**, 261. d) C. R. Alonso-Cruz, A. R. Kennedy, M. S. Rodriguez, E. Suarez, *J. Org. Chem.* **2008**, *73*, 4116. e) N. V. Rostovskii, A. V. Agafonova, I. A. Smetanin, M. S. Novikov, A. F. Khlebnikov, J. O. Ruvinskaya, G. L. Starova, *Synthesis* **2017**, *49*, 4478.

[18] a) For selected examples, see a) T. W. Miller, E. W. Tristram, F. J. Wolf, *J. Antibiot.* **1971**, *24*, 48. b) T. F. Molinski, C. M. Ireland, *J. Org. Chem.* **1988**, *53*, 2103. c) R. Kumar, L. I. Wiebe, E. E. Knaus, *Can. J. Chem.* **1996**, *74*, 1609. d) C. K. Skepper, T. F. Molinski, *J. Org. Chem.* **2008**, *73*, 2592.

[19] For a review on 2-halo-2*H*-azirine chemistry, see: T. M. V. D. Pinho e Melo, A. M. d'A Rocha Gonsalves, *Curr. Org. Synth.* **2004**, *1*, 275.

[20] a) A. Hassner, F. Boerwinkle, *Tetrahedron Lett.* **1969**, *10*, 3309. b) R. A. Valiulin, S. Mamidyala, M. G. Finn. *J. Org. Chem.* **2015**, *80*, 2740.

Layout 2:

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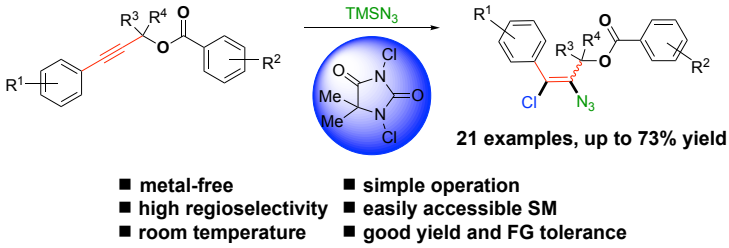

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